

Box DALTON (J. C.)

Surgeon C. H. Crane
THE
With Regards of
J. C. Dalton

ORIGIN AND PROPAGATION OF
DISEASE.

AN ANNIVERSARY DISCOURSE, DELIVERED BEFORE
THE NEW YORK ACADEMY OF MEDICINE,
NOVEMBER 20, 1873.

BY

JOHN C. DALTON, M. D.,

PROFESSOR OF PHYSIOLOGY IN THE COLLEGE OF PHYSICIANS AND SURGEONS, NEW YORK.

[PUBLISHED BY ORDER OF THE ACADEMY.]

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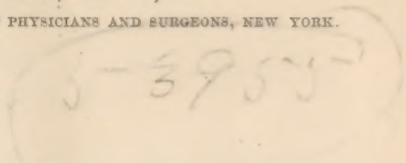
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ANNIVERSARY DISCOURSE.

MR. PRESIDENT AND FELLOWS OF THE NEW YORK ACADEMY
OF MEDICINE:

THE anniversary meeting of the Academy of Medicine may be regarded as a sort of annual conference, in which one of its members is deputed to offer to the Academy a short address upon some topic of general professional interest, and more or less appropriate to the time. Perhaps we can hardly employ the occasion to-night in a more suitable way than by endeavoring to see what, on the whole, is the direction in which medical thought is now most active; to cast the professional horoscope, so to speak, for the present, and to anticipate, as nearly as may be, what we are to expect from it in the immediate future.

Not that we should be willing to claim the gift of prophecy, or to place too much confidence in delusive flights of the imagination. Medicine is essentially a skeptical science, and very properly regards with disapproval any thing which claims her attention without offering, at the same time, unmistakable guarantees of respectability. But there may be a kind of anticipation which is really a scientific one. Within the past two or three years we have seen our own Meteorological Bureau triumph over what was proverbially the most difficult of all popular puzzles, and foretell the weather of each day with a certainty which has excited our surprise and admiration. With

telegraph-lines from all over the continent converging to the central office at Washington, the chief of the Bureau can trace, from hour to hour, the progress of a meteorological change, moving, with uniform or accelerated speed, from St. Paul to Milwaukee, from Milwaukee to Detroit, from Detroit to Buffalo; and he knows that within a given period it will reach New York, with almost as much certainty as though he stood on the top of a watch-tower and saw it coming. Within such limits as these it may perhaps be allowable sometimes to indulge in surmises, even in the strictest and most exacting of the natural sciences.

Is there any thing in the aspect and condition of any part of medicine to-day that looks like a change in the scientific barometer? Can we see such a tendency in the medical mind, at present, as would suggest what may fairly be called a new movement—in which successive ideas and discoveries are not only accumulating as heretofore, but in which they also seem to be taking, or about to take, a new interpretation; so as to give expression, in definite terms, to a doctrine which has heretofore had only a vague and uncertain existence?

If there be any one direction in which progress is now so marked as to constitute a dominant feature of the present state of medicine, and to embrace a practically new medical idea, I should say it was that of the *origin and propagation of disease by independent organic germs*. Perhaps it would be wrong to say that this doctrine is even yet distinctly formulated. It is certainly far from being definitely established as a general truth. Some very wild and reckless statements have been made in regard to it, by observers possessed of more zeal than knowledge; and some elaborate but baseless theories relating to the specific development and transformation of organic germs have been tried at the bar of scientific investigation, and, being convicted of incompetency, have suffered, accordingly, the just penalty of extermination. Perhaps the doctrine itself will also be finally abandoned. It may be that the evidence in its favor, which is yet only partial, will hereafter lose its special significance; and the appearances which now seem to

sustain it may come to be naturally explained in some other way. Still, there can be no doubt that the idea is at present entertained, and that it is by no means confined to the minds of careless or irresponsible theorizers. So far, it exists in the form rather of a scientific instinct than of a positive belief; and its gray light hangs about the edge of the medical horizon like the coming dawn of a new period.

Now, can this instinct of the medical mind be justified in any way? Are there any facts and discoveries, already established beyond the possibility of doubt, which have naturally led it in this direction, and which point, like the telegraphic reports of successive meteorological stations, to a continuous and definite movement of scientific pathology?

I think it really began many years ago, in the early investigation of parasitic diseases. Perhaps we can hardly include under this designation the effects produced by ordinary intestinal worms, like *tænia* or *ascaris*, because the animal and parasitic nature of these worms was perfectly palpable, and could not be mistaken by any one. But *scabies* was on a different footing. It was a contagious, eruptive affection, capable of spreading over a large portion of the body, and of giving the patient great discomfort; and, when it was found to be due simply to the presence and propagation of a parasitic insect, the discovery was a great achievement, and for the first time made it possible to have a distinct and rational comprehension of the origin of the disease, as well as of its propagation and means of cure. A remarkable circumstance in the history of our knowledge in regard to *Sarcoptes scabiei* is, that its discovery in the present century was in fact a rediscovery of something which had been known centuries before and long forgotten; or, at least, the method of finding the insect having been lost, the most eminent dermatologists of forty years ago had never seen it, and were really in doubt as to its existence. However, this uncertainty was terminated in 1834, by the Corsican student Renucci, and the study of its structure and development was afterward accomplished by Raspail and Bourguignon; so that our knowledge, both of the disease and its parasite, was then placed upon a permanent footing.

Perhaps the most suggestive part of this discovery related to the *reproduction* of the parasite, the manner in which the female lays her eggs in galleries excavated in the skin, and the time required for the hatching and dispersion of the young, because this showed a direct connection between the local spread of the disease and the increase, by ordinary sexual generation, of the young brood of the parasite. However, there was nothing very remarkable in the mode of this generation. The eggs of the female were deposited and hatched in the usual way, and the young sarcoptes came to resemble their parents after a very short and regular period of development.

But ten or fifteen years later a discovery was made with regard to some of the *internal* parasites which had a character of unexpected peculiarity: that was, the specific identity of two parasites formerly supposed to be distinct, namely, cysticercus and tænia. These two worms—so unlike in their size, their general configuration, and even in the species of animal which they inhabit—were shown by the researches of Siebold and Küchenmeister to be only different stages of growth of the same creature—one the encysted and quiescent, the other the intestinal and reproductive form. The well-known experiments carried on in this investigation showed furthermore the regular and natural conversion of these two forms into each other; and thus we came fully to understand that the existence of tape-worm in man was owing to his having eaten measly pork containing cysticercus, and that the pig became contaminated with cysticercus by devouring the eggs or the egg-bearing articulations of tænia solium. The knowledge of the alternation of generations and of the migration of parasites from one habitat to another at different periods of their development became in this way connected with the pathology and mode of propagation of certain well-known and perfectly distinct morbid affections.

But so far, perhaps, these morbid affections hardly deserved the name of diseases. They were simply local disorders, due to the presence of a parasitic intruder in the substance of the skin or in the cavity of the intestinal canal. It was another

thing to learn, some years later, that a microscopic parasite might diffuse itself generally throughout the system, and thus give rise to a rapid and fatal train of symptoms hardly distinguishable from those of any febrile constitutional disease. No doubt cases of infection by *Trichina spiralis* have always occurred, as frequently as they do now. But previous to the year 1850 the milder ones in all probability were supposed to be rheumatic in their origin, while the fatal cases passed for fevers of a typhoid character. There were even epidemics of the trichinous affection, as there are of typhoid fever and influenza; and, when the true character of the disease became known, it was perfectly evident how these epidemics originated and exactly how far they might extend. Each one was commenced by the slaughter and preparation for food of a trichinous pig; and the patients affected were precisely those who had introduced into their systems ever so small a portion of the infectious food.

In this instance, also, there was found to be an unexpected relation between two different forms of the same parasite. *Trichina spiralis* had been known since 1830: but it had yet been seen only in its quiescent, encysted form, embedded in the muscular tissue, without movement or reproduction. Consequently, though we were familiar with the worm itself, we knew nothing of the disease produced by it. Its new growth and active reproduction in the intestinal canal, the swarming emigration of its innumerable progeny, and the constitutional symptoms which followed, were a new revelation, and showed that the whole system, as well as a particular organ or tissue, might suffer from the effects of parasitic contamination.

In all the affections which have now been enumerated, the parasite is one of an animal nature, with regular generative apparatus and active sexual reproduction. But the last thirty years have seen a very remarkable advance also in our knowledge of the *vegetable* parasites. This has naturally coincided with a similar activity among scientific botanists in the study of the simpler forms of vegetation, the cryptogamic plants in general, and particularly of the microscopic fungi and algæ.

A little over half a century ago the species of flowering plants described by botanists were much more numerous than the cryptogams; but now the proportions of the two classes are reversed. In 1818, according to Mr. Cooke,¹ an eminent British botanist, "less than eighty of the more minute species of fungi, but few of which deserved the name of microscopic, were supposed to contain all then known of these wonderful organisms. Since that period microscopes have become very different instruments; and one result has been the increase of the 564 species of British fungi to 2,479. By far the greater number of the species thus added depend for their specific characters upon microscopical examination. At the present time the number of British species of flowering plants scarcely exceeds three-fourths of the number of fungi alone, not to mention ferns, mosses, algæ, and lichens."

A large proportion of these microscopic plants are parasitic upon other organisms; and for the earliest study of them, as connected with disease in the human subject, we are indebted to the dermatologists.

The first discovery of parasitic vegetation in cutaneous affections was by Schönlein, in 1839,² who found in the crust of favus cryptogamic vegetable filaments ramifying in the diseased growth. In 1841 Gruby made a similar observation,³ and described accurately both the mycelium filaments and the spores. He asserted them to be always present in cases of favus, and declared that the malady itself was essentially "nothing but a vegetation." The parasite thus described proved to be the same with that previously seen by Schönlein, and it was at last definitely known by the name of *Achorion Schönleini*.

Gruby continued his examinations, and in 1844 discovered a microscopic vegetation growing upon the skin, in a case of

¹ "Introduction to the Study of Microscopic Fungi," London, 1870, p. 45.

² Müller's Archiv for 1839; cited in Robin, "Végétaux Parasites," Paris, 1853, p. 477.

³ "Comptes Rendus de l'Académie des Sciences," 1841, tome xiii., pp. 72, 309.

porrigo decalvans;¹ and the same parasite, the *Trichophyton tonsurans*, has since been recognized as a constant accompaniment of tinea sycosis and tinea circinnata.

Finally, *Microsporon furfur* was discovered by Eichstedt, in 1846,² as a parasitic vegetation in tinea versicolor; so that within seven or eight years three distinct microscopic fungi were discovered and recognized as occurring in diseased conditions of the human skin.

Now, the first question which naturally came up in relation to the discovery was this: Is the microscopic fungus the cause of the disease, or is the disease the cause of the fungus? Either of these two suppositions might be the true one. In the first place, the fungus, by its accidental presence and growth in the skin, might excite all the irritation and morbid discharges characteristic of the malady. On the other hand, its presence might be altogether secondary, and a result of the morbid action instead of its cause. Every vegetable requires a soil suited to its growth. The fungus-germs might be incapable of fastening themselves upon the healthy skin, but might readily flourish in the decomposing mixture of inflammatory exudations. This question, in the earlier stages of the investigation, presented a real difficulty. Hensle, in 1840, believed that *Achorion Schönleini* was merely an incidental formation in the crust of favus, while Remak and others regarded it as the cause and essential element of the disease.

Now, how was this difficulty to be settled? If tinea tonsurans is always accompanied by trichophyton, and if trichophyton is never found upon the skin, except in some form of tinea, how can we tell which of these two is the cause and which the consequence of the other?

The test of this is twofold: 1. Inoculation of the parasite and reproduction of the disease; 2. Destruction of the parasite and cure of the disease.

Both of these tests have been successfully carried out. The inoculation of *Achorion Schönleini* was accomplished by

¹ "Comptes Rendus de l'Académie des Sciences," tome xviii., p. 583.

² Cited in Robin's "Végétaux Parasites," Paris, 1853, p. 438.

Remak,¹ in 1840, and subsequently by Bennett,² Hebra, Vogel, Bazin,³ Köbner and Deffis; that of *Trichophyton* by Deffis⁴ and Köbner;⁵ and, finally, that of *Microsporon*, by Köbner,⁶ in 1864. The fungus-spores, transplanted upon the skin of other individuals, or upon other parts of the skin of the patient, after a certain interval germinate and multiply, and so create a secondary focus of the disease. The contagious character of the malady is thus seen to depend, not upon a virus, in the old sense of the word, but upon the actual communication of reproductive germs, which give origin in their new location to a vegetative growth similar to the old. The vegetable growth, therefore, precedes the disease, and must be regarded as its cause rather than its consequence.

The actual transportation of these germs through the air is also a matter of demonstration. Lemaire⁷ placed glass jars filled with ice in a shallow basin, so that the condensed moisture of the atmosphere, deposited upon the cold sides of the glass, might trickle down and collect in the basin below. He then applied friction to the head of a boy with favus, near by, and found that the spores of *achorion* were floated by the air-currents for a distance of twenty inches into contact with the jars; and then, being entangled by the condensed moisture, were carried down into the basin. He sometimes found as many as thirty spores in a single drop of condensed moisture.

The second part of the test is equally well established. I presume that dermatologists are now fully agreed that, for all cutaneous affections known to be characterized by the presence of a microscopic fungus, the one essential element of

¹ Cited in Robin; "*Végétaux Parasites*," Paris, 1853, p. 477.

² "*Principles and Practice of Medicine*," New York, 1867, p. 850.

³ "*Affections cutanées parasites*," Paris, 1858, p. 56.

⁴ Bazin, "*Affections cutanées parasites*," p. 147.

⁵ Schmidt's "*Jahrbücher*," cxxvi., p. 260.

⁶ Cited in Neumann's "*Handbook of Skin Diseases*," translated by Dr. L. D. Bulkley, New York, 1872, p. 434.

⁷ "*Comptes Rendus de l'Académie des Sciences*," 1864, tome lix., p. 127.

cure is the application of some parasiticide which shall destroy the vitality of the fungus. Iodine, sulphurous acid, or mercurial bichloride, by killing the vegetable, as sulphur-ointment kills the animal parasite of scabies, in simpler cases absolutely puts an end to the disorder, and in the more complicated ones leaves behind only secondary symptoms, which have no longer any specific or contagious character. Of course there are various points relating to these affections which are still more or less in doubt. Some microscopic cutaneous fungi have been described as distinct species, which have not received general recognition, and some observers are disposed to question whether the three principal ones may not all be simple varieties or forms of development of the same plant.

But there are similar points of difference still existing among scientific botanists with regard to microscopic fungi in general; and I believe that the three principal facts of (1) specific parasitic vegetation as a cause of cutaneous disease; (2) its propagation by the transport and germination of spores; and (3) its treatment and cure by parasiticide applications, may now be regarded as wholly beyond a reasonable doubt.

I have already alluded to the remarkable activity of botanical research of late years in the department of cryptogamic vegetation. The most striking results have been attained by these investigations, in increased knowledge of the modes of development and reproduction of these organisms. The phenomena of the so-called alternation of generations and of migration from one habitat or locality to another, are by no means confined to animal parasites. On the contrary, the most remarkable instances of both are to be found in cryptogamic vegetables. Fungi formerly regarded as distinct species, and even as belonging to different genera, are seen to be successive forms of the same plant, following each other in definite order through the regular cycle of their annual reproduction.

The three fungi, known as *Trichobasis*, *Puccinia*, and *Æcidium*, appear in succession, as different members of the same specific generation, upon the cereal grains in summer

and in autumn, and upon the barberry in the spring; while corresponding differences are to be seen in their spores and mode of germination at these different epochs.

It would perhaps be difficult to imagine a scientific pursuit less likely to produce any thing of value for practical medicine than the study of microscopic fungi growing as parasites upon other vegetables. And yet, if it should finally turn out that these minute researches are preliminary to the discovery of a means for preventing or controlling an epidemic of scarlatina, we can say with truth that such a result would not be more remarkable than many which have actually followed from purely scientific investigations in chemistry and physics.

At all events, it is certain that these botanical discoveries have had an important influence in directing medical research in the path which it is now following. It could hardly be otherwise, from the moment they were found to have a direct connection with certain epidemic diseases in the vegetable world, some of which are of great practical consequence to us, as affecting the annual supply of food.

Let me remind you of the history of our knowledge in regard to the disease known as *potato-rot*.

This disease first made its appearance, so far as we know, about thirty years ago. The most destructive season of that epidemic in this country was in 1844.¹ Previously to that time, the annual crop of potatoes in the United States amounted to over one hundred million bushels; but, in consequence of the blight, it was reduced in some parts of the country to one-half or even to one-quarter of the ordinary yield.²

In 1845, it showed itself in England, Scotland, and Ireland, and spread with great rapidity. This is the account of it given by Mr. Cooke,³ one of the highest authorities on that subject:

¹ *American Quarterly Journal of Agriculture and Science*, January, 1845.

² "Patent-Office Reports, Department of Agriculture," 1856.

³ "Introduction to the Study of Microscopic Fungi," London, 1870, pp. 144, 146.

"It first appeared in the Isle of Wight, in the middle of August; a week afterward, it had become general in the south of England, and at the end of a fortnight there were but few sound samples of potatoes in the London market. The course of the disease was this: In the month of July or August the leaves of the vines would be suddenly seen to be marked with black spots. They then began to wither, and give off an offensive odor, and the disease spread so rapidly that the whole vine would be blighted in a few days, and a field, which had before been covered with a luxuriant growth, at the end of a fortnight was merely a scene of desolation, and looked as if it had been struck by a severe frost. If the potatoes were immediately dug out of the ground, many of them were found already partially decayed, or touched with brownish and softened spots."

The disease broke out again in 1854 and 1855, and was destructive in the State of New York, in Rhode Island, Massachusetts, Ohio, Illinois, and at various other points;¹ and about 1865, or ten years later, it made its appearance for a third time. I am told by an old and experienced farmer of Washington County, New York, that in 1864 and 1865 the potato crop in that region was practically destroyed; so that often in a twenty-acre field there would not be a single good potato. Potatoes were usually to be had at that place for seventy-five cents per bushel, but in those years they were in some cases sold at eight dollars per bushel, for farmers' consumption.

This destructive malady was at last found to be due to the ravages of a microscopic fungus, called, from its mode of fructification and its injurious effects, the *Peronospora infestans*.

The fungus has a mycelium of fine, cylindrical, ramifying tubes. Its fructifying part consists of filaments which stand up vertically from the mycelium, dividing at the end into four or five branches, and each branch bears upon it several successive swellings, making a kind of sausage-like chain, whence its name of "*Peronospora*." At the end of each chain there is a

¹ "Patent-Office Reports, Department of Agriculture," 1856; "Massachusetts State Board of Agriculture," 1856.

complete oval spore, and the spore, when ripe, detaches itself and germinates, to produce again a new mycelium.

When the peronospora is placed in contact with the leaves of a potato-vine, its filaments penetrate into and through the epidermic cells, and so reach the intercellular tissue of the leaf and stem; and there they continue to grow, producing a rapid withering and blight. When the parasite has attained a certain growth, it begins to fructify. Its upright filaments burst through the pores of the leaves, and are crowned with the characteristic chain of spores. Each spore, when ripe, if supplied with moisture, produces six or seven secondary zoospores, armed with long vibrating cilia, and capable of a rapid spontaneous motion. After moving about for a short time, the zoospore becomes quiescent, throws out an elongated filament, and germinates afresh.

It is no doubt in this way that the germ of the parasite reaches the tuber of the potato at the root of the vine. For, if sound potatoes be placed in the ground, and the surface of the soil be sprinkled with the spores of peronospora, and then watered from time to time, the potatoes are found to be infested with the disease in about ten days.¹

So the fructification of the fungus naturally takes place upon the surface of the leaves of the potato-vine. The spores fall off, are carried by the rain into and through the soil, and so reach the potatoes beneath. Next year, when the infected potato-eyes are planted, germination begins again, the mycelium filaments grow upward through the stem and leaves, and in July or August fructification appears on the exterior as before.

This species affords a good example of the extreme fecundity of the parasitic fungi. It has been estimated that, on the under surface of a potato-leaf, one square line is capable of producing over three thousand spores. Each spore supplies at least six zoospores; so that from one square line we may have nearly twenty thousand reproductive bodies, each capa-

¹ Robin, "Traité du Microscope," Paris, 1871, p. 967.

ble of originating a new mycelium; and a square inch of surface may yield nearly three million such bodies.

The mycelium filaments can penetrate the cellular tissue of a leaf in twelve hours, and, when established there, may grow and bear fruit in eighteen hours longer, while the spores are perfected and ready to germinate in twenty-four hours after they have been detached and placed in water. This fully explains the rapidity with which the disease is known to spread.

The subject of internal vegetable parasites is of the greater importance, because we now know that they may attack animals as well as plants. The best illustration of these affections is perhaps the disease which, under the name of *pébrine*, has been so destructive to the silk-worm in France. Eight or ten years ago its effects were so serious that, in 1865, the annual production of silk in that country was reduced to less than one-sixth of its former average, and the loss in money value for that year alone amounted to twenty million dollars.¹ It was due entirely to the influence of a microscopic vegetation, which destroyed the silk-worm, and was readily communicated to the neighboring broods.

It is plain, therefore, that the study of parasitic diseases, for many years, has been increasing in development and becoming of greater importance in general pathology. From being confined, as at first, to a few cases of local disorder, it has now come to embrace a great variety of morbid affections. It has demonstrated the close connection existing between animal and vegetable pathology, and it has shown that severe and even fatal constitutional disorders of the animal frame may result from the internal growth of microscopic parasites of a vegetable nature. And these facts have been ascertained by patient microscopic investigation, and laborious experiment on the development of eggs and spores, and the phenomena of infection and contagion. It cannot be denied that the results, so far, are genuine.

We now come to a part of the subject which may seem to be less directly connected with medical doctrines; and yet it

¹ Tyndall, "Fragments of Science," New York, 1872, pp. 288.

is one which, if it really have a bearing on pathology, gives to the whole question a character of still greater importance. That is, the true nature of the process of *fermentation*.

The more essential phenomena of fermentation have been known from time immemorial. If we add to a solution of sugar, or to any clear vegetable juice containing sugar, a small portion of yeast, and keep the mixture in a moderately warm place, after a few hours of apparent inactivity, certain remarkable changes take place it: 1. The liquid becomes uniformly turbid. 2. It is more or less agitated by minute bubbles of gas, which are generated in its interior, rise to the surface, and escape there. 3. The sugar gradually disappears from the solution, and alcohol takes its place. 4. When all the sugar has been thus consumed, the gas-bubbles cease to rise, the liquid again becomes clear and quiescent, its turbid contents being slowly deposited in a whitish layer at the bottom; and, 5. This deposit is found to be itself a layer of yeast, often much greater in quantity than that originally added, and capable of exciting the same kind of fermentation in another saccharine liquid.

Beside this, chemical investigation has shown that the gas evolved is carbonic acid, and that the weight of the sugar which disappears is accounted for, within reasonable limits of accuracy, by that of the carbonic acid and alcohol produced, with a little glycerine and succinic acid formed at the same time. It is therefore a chemical transformation, in which the elements of the sugar are separated from their combination, and rearranged to form other non-nitrogenous compounds.

But it is a chemical change which will not take place spontaneously. It requires the presence of yeast artificially added, or of a natural ferment, present in the vegetable juice. The theory of fermentation formerly in vogue was, that the nitrogenous matter in solution in the yeast excited, by its own molecular changes, the decomposition of the sugar; taking by itself no direct part in the chemical phenomena, and neither absorbing nor discharging any of the materials of the solution.

In enumerating these facts I do not always follow the ex-

act chronological order in which they were discovered, nor do I wish to take up your time in alluding to all the details and varieties of fermentation. It will be sufficient for our present purpose to bear in mind simply the main features of the process, namely, the addition of ferment to a saccharine liquid, turbidity of the solution, decomposition of the sugar, appearance of alcohol and carbonic acid, and, finally, reproduction of the ferment.

Two hundred years ago Mr. Anthony Leeuwenhoeek was investigating all sorts of natural objects with his newly-constructed microscopes, consisting each "of a very small double convex glass, let into a socket between two silver plates." He examined the blood-globules, the capillary vessels, the spermatic corpuseles, the structure of wood, of hair, of teeth; and with the same instruments he saw in yeast little globules collected into groups of three or four together.¹ But he had too many other novelties, all attracting his attention together, to spend much time on any one of them, and he did not learn the nature or specific characters of the globules of yeast; he only determined the bare fact of their existence.

But in 1837 the French chemist Cagniard-Latour² examined the yeast-globules with more care. He measured their size, and found them to be at most $\frac{1}{2500}$ of an inch in diameter. He declared that they were of a vegetable nature, and that they multiplied by the process of budding. He called attention to the fact that during the fermentation of beer the ferment increases in quantity, producing at the end of the process six or seven times as much yeast as was introduced at the beginning; and he first broached the idea that "it is probably by some effect of their vegetation that the yeast-globules destroy the equilibrium of the elements of the sugar."

The theory, however, was at that time premature, and it did not meet with general acceptance. The existence of the yeast-plant, so far as then known, was an isolated fact, confined to the single case of fermenting beer. The opposite theory, of

¹ "Philosophical Transactions," 1681, p. 507.

² "Annales de Chimie et de Physique," 1838, tome lxxiii., p. 216.

the catalytic action of an albuminous liquid, was maintained by Liebig with all the force of his remarkable genius, and was consequently almost universally adopted. The yeast-plant was thought to be an incidental growth in the fermenting fluid, and not to have any direct or important connection with the process itself.

About fifteen years ago a new epoch was inaugurated in the history of fermentation by the brilliant researches of Pasteur. The existence and growth of a fungoid vegetation were now found not to be confined to the single case of beer-yeast, but to be a general fact common to the alcoholic fermentation of beer, wine, and bread, and also to a variety of other kinds, such as the viscous, butyric, and acetic fermentations. The fungus itself was industriously studied in its different genera and species, with their specific modes of growth and reproduction, like those of any other natural family of plants; so that the *Saccharomyces cerevisiæ*, or the yeast-fungus of beer, can now be distinguished from the other species of alcoholic ferments, as well as from the fungi of other kinds of fermentation.

The different view thus introduced is most distinctly expressed by Pasteur himself. "According to the old theory," he says, "fermentation is a process correlative with death, and depends on the decay of albuminous matter; according to the new one, it is correlative with life, that is, the active growth and development of the fungous vegetation. . . . The yeast-globules are actual living vegetable cells, capable of producing the transformation of sugar, just as the cells of the mammary gland in a living animal transform the ingredients of the blood into the ingredients of the milk."

The discussions on this subject, which lasted for ten years, took a very wide range, and especially became connected with the kindred topic of "spontaneous generation." The experiments of Pasteur and others showed that the germs of the yeast-plant may be disseminated by the atmosphere, and that the same precautions which exclude the introduction of germs from without into a fermentable liquid also exclude the process

of fermentation itself; so that we can now accept with confidence the double fact—1. That the growth and reproduction of the yeast-fungus will take place only in a fermentable liquid; and, 2. That such a liquid will ferment only when the yeast-fungus is present and in a state of active development.

The revolution in opinion on this point was so complete that, in regard to the alcoholic fermentation at least, its essential results were finally accepted by Liebig himself. In his last treatise on fermentation, published in 1871, he says: "There no longer remains any doubt as to the nature of the ferment of beer and wine. It is a cryptogamic vegetation, more or less fully developed. . . . We may conclude that the albuminous matters of the yeast take part in its action upon the sugar, and it is evident that these albuminous matters acquire their property of exciting fermentation by becoming an actual constituent of the yeast itself."

Consequently, the fermentation of a saccharine liquid is the result of vegetative activity. We add to the liquid a few cells or spores of the yeast-fungus. These grow and multiply, and the turbidity of the liquid is due to their increase and dissemination. They decompose its sugar, appropriate some of its elements, and leave as a result alcohol and carbonic acid. When all the sources of their nourishment are exhausted, fermentation stops, and the liquid becomes clear, the yeast-cells subsiding to the bottom. But the ferment has in the mean time been reproduced, like so much grain which has been sown, raised, and harvested; and a little of the deposit left at the bottom of the vessel, if introduced into another saccharine liquid, will in turn reproduce the process of fermentation.

It is impossible not to perceive a certain analogy between the general phenomena of fermentation and those of contagious and infectious diseases. The period of incubation which intervenes between the exposure to a contagion and the appearance of the malady—the regular course of the symptoms—their natural termination within a definite time, and

¹ "Annales de Chimie et de Physique," 1871, tome xxiii., pp. 9, 10.

the evident reproduction of the contagious element—all these facts were so many points of resemblance, which could not escape the attention of medical observers. The analogy, indeed, has long been recognized in our nomenclature; and the term *zymotic diseases* cannot mean any thing else than diseases depending upon some cause which acts after the manner of a ferment. But this name was adopted only as a matter of convenience, and was understood altogether in a symbolical sense. Of late we have begun to suspect that, after all, it may be simply the expression of a literal fact.

A similar order of discoveries has recently been made with regard to *putrefaction*. This has a more immediate connection with pathology than fermentation, because it is a change which takes place in animal substances, while fermentation, at least in its simpler forms, relates mainly to products of a vegetable origin.

Putrefaction was formerly regarded as the natural and inevitable decomposition of dead animal matter when exposed to the oxygen of the atmospheric air. But in reality something else is necessary. In every putrefying liquid there are a growth and development of minute living organisms. If we take a clear solution of any nitrogenized animal or vegetable matter and expose it to the air at a moderate temperature, after a short time it becomes turbid. This turbidity is the first evidence of commencing putrefaction, and it is exactly analogous to the turbidity of a saccharine liquid which are beginning to ferment. Microscopic examination shows that it is due to the presence of innumerable bacterium-cells, $\frac{1}{8,000}$ of an inch long, by $\frac{1}{40,000}$ of an inch wide, moving in every direction, and multiplying by a rapid process of subdivision. As long as putrefaction goes on, so long the bacteria multiply. When it comes to an end the liquid becomes clear, and there is a quiescent layer of bacteria deposited upon the bottom. The least particle of this layer, added to another albuminous liquid, will excite putrefaction in it, and will produce a new development of bacterium-cells, the quantity of which is limited only by that of the albuminous matter which serves for their nourishment and growth.

Now, bacteria are the smallest and most obscure of living things. Their minute size alone is a sufficient obstacle, with our present microscopes, to their complete and satisfactory study in all particulars. Nevertheless, some important facts have been established with regard to them. In the first place, they are undoubtedly vegetable in their nature, and consist of cells which multiply by division, not by budding. They require for their growth a temperature between the limits of freezing and boiling water. They consist of a protoplasmic matter, surrounded by an envelope of vegetable cellulose. They live upon nitrogenized and carbonaceous organic matters in solution, and, like other colorless plants, absorb oxygen and exhale carbonic acid. They present a variety of genera and species, which may be distinguished from each other with some approach to accuracy; and, of these, *Bacterium termo* is the most constant and indispensable inhabitant of putrefying infusions.

As to the true relations between bacteria and putrefaction, almost the same course of inquiry has been followed as in the case of the yeast-fungus and fermentation. At first regarded simply as an incidental accompaniment of the process, they are now considered as its essential and immediate cause. This view is distinctly stated by Dr. Ferdinand Cohn, to whom we owe more definite information on the natural history and microscopic characters of bacteria than to any other observer. Dr. Cohn is a professed scientific and experimental botanist, and director of the Institute of Vegetable Physiology, at Breslau. He was the first to establish, twenty years ago,¹ the vegetable nature and structural relations of bacteria, and he has recently contributed largely to our knowledge of their classification and general physiology.² According to him, the putrefaction of nitrogenous organic matters is neither a spontaneous *post-mortem* decomposition, nor is it a simple oxidation under the influence of the atmosphere. "It is rather a chemical process caused by the action of *Bac-*

¹ "Nova Acta Academiæ Carolæ-Leopoldinæ," lib. xxiv., p. 1.

² "Beiträge zur Biologie der Pflanzen," 1872, No. ii., p. 127.

terium termo. Just as sugar is never converted spontaneously into alcohol and carbonic acid, and is brought into fermentation only by the yeast-fungus, so nitrogenous organic matters never putrefy of themselves, but only by means of the vital activity and multiplication of bacteria. . . . We may therefore," he says, "apply Pasteur's doctrine also to the decomposition of animal matters, and may adopt as true the seeming paradox that *putrefaction is an incidental phenomenon, not of death, but of vitality.*"

The proof that living bacteria are the cause of putrefaction, and not merely its accompaniment, is that a putrescible liquid which has been sufficiently boiled and received in a superheated glass vessel may be kept in contact with the atmosphere indefinitely without putrefaction, provided the access of bacteria be prevented by a plug of cotton-wool. But, if the minutest portion of any liquid already infected with bacteria be added, putrefaction at once begins. Dr. Burdon-Sanderson, by a series of very important experiments in 1871,¹ has established the fact, which is also confirmed by the researches of Cohn,² that contamination by the germs of bacteria takes place, as a general rule, not directly from the atmosphere, but by means of water and unclean moist surfaces; while, on the other hand, the germs of the mould-fungi, like penicilium and mucor, are more or less constantly present in the air, and so readily gain access to organic substances, even in a dry atmosphere. Consequently, such substances, if properly protected against bacteria, do not putrefy, but, on the other hand, may become covered with a mould-fungus. Dr. Sanderson even cut out the muscular tissue of the thigh of a recently-killed Guinea-pig, and hung it up under a bell glass, using for this purpose a knife and hooks which had just been subjected to the flame of a Bunsen burner, but taking no other precautions; and for thirty-one days, though the exposed tissues were over-

¹ "Thirteenth Report of the Medical Officer of the Privy Council," London, 1871.

² "Beiträge zur Biologie der Pflanzen," No. ii., p. 189.

grown with penicillium, there was no development of bacteria, and no evidence of putrefaction.

The natural history of bacteria is especially connected with the question of spontaneous generation, because they are the only class of organisms now remaining in which reproduction by spores has not yet been discovered, and because they appear so promptly and abundantly in all putrescible liquids under ordinary exposures.

Whatever may be the difference of opinion, therefore, with regard to the possibility of spontaneous generation within limited and exceptional conditions, there is hardly a doubt remaining that as a rule, in the regular operations of Nature, the bacteria or their germs are, in point of fact, conveyed from one putrefying substance to another, and that putrefaction is a process excited by contagion, and accomplished only by the growth and nutrition of bacteria.

It was an important discovery when it was found, ten years ago, that bacteria might be developed in the interior of the living animal organism. In 1863 and 1864, Davaine¹ showed that in the disease of sheep, known in France as "charbon" or "sang de rate," and called by the Germans "milz-brand," the blood of the affected animal, during life, contained bacteria. He showed that the disease might be communicated by inoculation to other animals, always with a fatal result, and always with the development of bacteria in the blood previous to death. He afterward² extended the same observation to cases of malignant pustule, which he declared to be one form of the "sang de rate" disease.

In 1868 Vulpian³ found that a fatal disorder might be produced in frogs by the administration of cyclamine; that the malady was accompanied by the development of bacteria in the blood, and that inoculation of this blood reproduced the disease in other healthy animals of the same species.

¹ "Comptes Rendus de l'Académie des Sciences," tomes lvi., lix.

² "Comptes Rendus," 1865, tome lx., p. 1297.

³ "Archives de Physiologie Normale et Pathologique," 1868, p. 466.

About the same time, Professors Coze and Feltz,¹ formerly of the University of Strasbourg, had been making researches in a similar direction. They injected putrescent liquids into the veins or subcutaneous tissue in dogs and rabbits, producing in this way a fatal artificial septicæmia; and they found that bacteria were developed in the blood of the animal simultaneously with the appearance of the febrile condition. But the effect produced did not stop there. The blood of such an animal, though not itself putrid, had become infectious, and would excite septicæmia in another animal by inoculation. A still further remarkable result was obtained from these experiments: "By reproducing in this manner," the authors say, "several successive inoculations, it becomes evident that the infectious element is at last more active than the putrescent matters themselves. Injection of putrescent liquids is not so rapidly fatal as inoculation of the blood of an animal already infected."

These facts have been confirmed by the observations of Davaine and Vulpian, which show the extraordinary activity of infectious blood, even at a high degree of dilution. Davaine² found that putrefied bullock's blood, injected into the subcutaneous tissue of the rabbit, was rarely fatal in doses of less than $\frac{1}{100}$ of a drop, and never so in less than $\frac{1}{2000}$. But a series of twenty-five successive inoculations showed that septicæmia, once established, could be transmitted to the healthy rabbit by a dose of infectious blood so diluted that it represented only one trillionth part of a drop. Vulpian³ injected a rabbit with infectious serum, and produced death in twenty hours. A second rabbit was inoculated with the blood of the first, diluted to $\frac{1}{50}$, and died in twenty-four hours. A third rabbit was inoculated with the blood of the second, diluted to $\frac{1}{1000}$ and died in twenty-three hours. A fourth animal, inoculated with the blood of the third, diluted to $\frac{1}{10000000}$, died in

¹ "Recherches cliniques et expérimentales sur les Maladies infectieuses," Paris, 1872.

² "Bulletin de l'Académie de Médecine," Septembre 17, 1872.

³ *Gazette Médicale de Paris*, 1873, No. 3, p. 30.

fifty-two hours; while the fifth, inoculated with a dilution of $\frac{1}{1,000,000,000}$, became ill, but finally recovered.

In cases of septicaemia, therefore, the bacteria really multiply in the circulation during life; and the small quantity of infectious blood necessary to produce the disease is explained by their singular activity of reproduction.

These experiments certainly bring the study of morbid contagion into very close relationship with that of putrefaction and fermentation; and there is no doubt that the analogies between them become more distinct and suggestive at every step of the investigation. It only remains to show that the same results will apply to diseases of more regular type and more familiar occurrence.

If we were to choose any single morbid affection as a fair representative of the whole class of contagious disorders, I suppose small-pox would be the one selected. Its virulence, the certainty of its communication, the abundance of infectious matter generated, the regularity of its symptoms, and the definite periods of its incubation and development, all make it, so to speak, a kind of exponent of the essential qualities of infectious disease. Beside this, its singular relations to vaccine give it a peculiar interest; and the vaccine affection also, though milder in its symptoms, is hardly less marked as a contagion than small-pox itself. Conclusions derived from experiments with either must be of great value in regard to the study of contagion as a whole.

The first definite experiments in regard to the contagion of vaccine we owe, I think, to Chauveau.¹ He endeavored to ascertain whether the contagious principle of vaccine lymph were in its liquid or in its solid portions. For this purpose he treated vaccine lymph by the process of diffusion. The result showed that the contagious property of the lymph does not reside in its liquid part, but in its solid corpuscles and granulations. The liquid withdrawn by diffusion, though always found to contain abundance of albuminous matter in solution,

¹ "Comptes Rendus de l'Académie des Sciences," 1868, tome lxxvi., p. 289.

failed when used for vaccination ; while that containing the solid granules possessed its normal activity and succeeded as fully as the fresh lymph. The results of these diffusion experiments were confirmed by those of Dr. Burdon-Sanderson,¹ performed subsequently.

Chauveau also adopted a second plan for investigating the same point, namely, that by dilution. The significance of this test depends on the following consideration : If the real vaccine virus be a fluid, it is of course uniformly distributed through all parts of the lymph ; and, if this lymph be diluted to any extent, the fluid virus will still be equally disseminated throughout the whole. When the dilution becomes so great as to extinguish the activity of the virus, this activity ought to diminish and disappear at the same time uniformly through all parts of the liquid. On the other hand, if the contagious principle reside in the solid particles, each one of which is capable of reproducing its kind, these particles will only be separated from each other by the dilution, and made less likely to be taken up in the drop used for vaccination. But, if one of them should be so taken up, it would still produce its full effect. In this case, the number of successful vaccinations would diminish in proportion to the dilution, and the number of failures would increase. But every vaccination which failed would fail completely, and every one which succeeded would produce a normal result.

Chauveau's experiments showed that the latter supposition was correct. Vaccine lymph might be diluted with from two to eighteen times its weight of water without sensibly losing in efficacy ; and in one case the experimenter obtained a single pustule from a number of vaccinations made with lymph diluted to $\frac{1}{100}$. He obtained, however, the most remarkable results with the lymph of sheep-pox, upon which he experimented largely.² He inoculated the same animal, by twenty-one punctures, with poek-lymph diluted to $\frac{1}{500}$; and of these

¹ "Twelfth Report of the Medical Officer of the Privy Council," London, 1870, pp. 233, 235.

² "Comptes Rendus," 1868, tome lxxvii., p. 749.

twenty-one inoculations eight failed, while thirteen gave origin to full-sized pustules. He then diluted the pock-lymph at once to $\frac{1}{100,000}$; and, with this diluted lymph, out of twenty inoculations he obtained only a single pustule, but that pustule presented its normal features, and went through the usual stages of development.

The active properties of the lymph of vaccine and variola, therefore, do not reside in its liquid ingredients, but in its solid corpuscles. These corpuscles, which were already observed by Chauveau and Burdon-Sanderson, have been recently examined and described with great care by Dr. Cohn.¹ This observer adopted every precaution against the introduction of foreign elements into the lymph. Some children with healthy vaccine vesicles were brought to the Botanical Institute, the vesicles opened with a new, unused lancet, the lymph taken up by aspiration in a recently-heated capillary glass tube, dropped upon a microscope-slide, and fitted with a glass cover, both the slide and cover having just been thoroughly cleansed with ammonia and boiling water. The edges of the cover were then lacquered down, to exclude the air, and the lymph-corpuscles examined at successive intervals of time.

According to Dr. Cohn's observations, these corpuscles are single cells of a spherical form, not more than $\frac{1}{25,000}$ of an inch in diameter. They belong to the genus *Micrococcus*, and those of the vaccine lymph are designated by the name of *Micrococcus vaccinae*. They increase in numbers if kept at the temperature of the living body, forming chains and groups of associated articulations. Dr. Cohn finds similar bodies in the fluid of small-pox vesicles, identical in size and appearance with those of the vaccine lymph. "We must, therefore," he says, "for the present regard the pock-lymph corpuscles as living and independent organisms, belonging to the smallest and simplest of all living things, which multiply, without formation of mycelium, by cell-division alone, and perhaps also by the production of resting spores."

¹ "Organismen in der Pockenlymphe." *Archiv für pathologische Anatomie und Physiologie*, 1872, pp. 55, 229.

Finally, another kind of micrococcus has been described by Dr. Oertel,¹ of Vienna, and by Prof. Ebert,² of Zürich, as constantly present in cases of diphtheria; and both observers have found that its inoculation in different parts of the body in healthy animals produces a diphtheritic malady, having its starting-point at the place of inoculation.

The contributions to medical literature on this subject have increased of late with unusual rapidity. Since the beginning of 1870 more than two hundred distinct publications have made their appearance, either in the medical journals, or as separate volumes, on septicæmia and diphtheria, on micrococcus and bacteria, the ferment-corpuscles, fermentation and putrefaction, their relation to contagion and infection, and kindred topics. Many of these essays are extremely important, others of more or less doubtful value. I have not attempted to notice them all, but only those which seem to have really established some new facts relating to the origin and propagation of disease. Should the discoveries of the next ten years continue to lead in the direction now indicated, it will illustrate more fully than ever the intimate relation which exists between all the branches of medicine and natural science; for it will show how large a part of human pathology is connected with the general physiology of vegetative life.

¹ "Deutsches Archiv für klinische Medicin," 1871, B. viii., p. 242.

² "Zur Kenntniss der bacteritischen Mykosen," Leipzig, 1872.

